

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
16 August 2001 (16.08.2001)

PCT

(10) International Publication Number
WO 01/58891 A3

(51) International Patent Classification⁷: C07D 401/04,
211/60, 487/08, 207/16, 401/12, 405/12, 409/12, 277/06,
211/62, 205/04, A61K 31/496, A61P 25/28

(74) Agents: MARKS, Andrew: Vertex Pharmaceuticals Inc.,
130 Waverly Street, Cambridge, MA 02139-4242 et al.
(US).

(21) International Application Number: PCT/US01/04210

(22) International Filing Date: 9 February 2001 (09.02.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/181,944 11 February 2000 (11.02.2000) US
60/247,330 10 November 2000 (10.11.2000) US

(71) Applicant (for all designated States except US): VERTEX
PHARMACEUTICALS INCORPORATED [US/US];
Patent Department, 130 Waverly Street, Cambridge, MA
02139-4242 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): TOMLINSON,
Ronald [US/US]; 317 Diconza Boulevard, Marlborough,
MA 01752 (US). LAUFFER, David [US/US]; 254 Taylor
Road, Stow, MA 01775 (US). MULLICAN, Michael
[US/US]; 110 Parker Road, Needham, MA 02194 (US).

(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ,
DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ,
NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,
TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF,
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

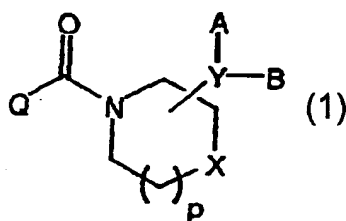
— with international search report

(88) Date of publication of the international search report:
25 April 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/58891 A3

(54) Title: PIPERAZINE AND PIPERIDINE DERIVATIVES FOR TREATMENT OR PREVENTION OF NEURONAL DAMAGE



(57) Abstract: The present invention relates to piperazine and piperidine derivatives of Formula (1), with Q, X, Y, A, B and P as defined herein, which are especially useful for treating or preventing neuronal damage, particularly damage associated with neurological diseases. These compounds are also useful for stimulating nerve growth. The invention also provides compositions comprising the compounds of the present invention and methods of utilizing those compositions for treating or preventing neuronal damage or for stimulating nerve growth.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/04210

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07D401/04 C07D211/60 C07D487/08 C07D207/16 C07D401/12 C07D405/12 C07D409/12 C07D277/06 C07D211/62 C07D205/04 A61K31/496 A61P25/28		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07D A61K A61P		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, WPI Data, CHEM ABS Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 811 434 A (SU MICHAEL ET AL) 22 September 1998 (1998-09-22) cited in the application cpds. (I) - (IV) abstract	1,11,16, 17
A	EP 0 333 522 A (MITSUI TOATSU CHEMICALS) 20 September 1989 (1989-09-20) cpds. (I) abstract	1,11,16, 17
A	US 5 290 793 A (FUKAZAWA NOBUYUKI ET AL) 1 March 1994 (1994-03-01) abstract; claim 1	1,11,16, 17
A	US 5 232 923 A (FUKAZAWA NOBUYUKI ET AL) 3 August 1993 (1993-08-03) the whole document	1,11,16, 17
-/-		
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
* Special categories of cited documents:		
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>*A* document defining the general state of the art which is not considered to be of particular relevance</p> <p>*E* earlier document but published on or after the international filing date</p> <p>*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>*O* document referring to an oral disclosure, use, exhibition or other means</p> <p>*P* document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>*Z* document member of the same patent family</p> </div> </div>		
Date of the actual completion of the international search <div style="text-align: center; font-weight: bold;">28 September 2001</div>		Date of mailing of the international search report <div style="text-align: center; font-weight: bold;">10/10/2001</div>
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl. Fax: (+31-70) 340-3016		Authorized officer <div style="text-align: center; font-weight: bold;">Diederens, J</div>

INTERNATIONAL SEARCH REPORT

Inte. onal Application No.

PCT/US 01/04210

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>US 4 374 990 A (WEBER ROLF-ORTWIN ET AL) 22 February 1983 (1983-02-22) cited in the application compound 30</p>	1

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-9 (partially), 11-24 (partially)

Present claims 1-9 (partially) and 11-24 (partially) relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely the compounds actually exemplified in the description.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/04210

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 5811434	A	22-09-1998	AU 5439698 A	03-06-1998
			BR 9712947 A	28-03-2000
			CN 1239435 A	22-12-1999
			EP 0941112 A1	15-09-1999
			JP 2001503777 T	21-03-2001
			NZ 335395 A	29-07-1999
			PL 333242 A1	22-11-1999
			WO 9820892 A1	22-05-1998
EP 0333522	A	20-09-1989	JP 1238524 A	22-09-1989
			JP 1963633 C	25-08-1995
			JP 6096520 B	30-11-1994
			JP 1984716 C	25-10-1995
			JP 2053767 A	22-02-1990
			JP 7020929 B	08-03-1995
			AU 602628 B2	18-10-1990
			AU 3144389 A	21-09-1989
			DE 68917499 D1	22-09-1994
			DE 68917499 T2	09-02-1995
			DK 130389 A	19-09-1989
			EP 0333522 A2	20-09-1989
			FI 891227 A	19-09-1989
			KR 9108665 B1	19-10-1991
			NO 891191 A	19-09-1989
			NZ 228329 A	23-12-1991
			US 5232923 A	03-08-1993
			JP 1942043 C	23-06-1995
			JP 2152950 A	12-06-1990
			JP 6078286 B	05-10-1994
US 5290793	A	01-03-1994	JP 1931219 C	12-05-1995
			JP 3099046 A	24-04-1991
			JP 6060141 B	10-08-1994
			AU 625163 B2	02-07-1992
			AU 6224990 A	21-03-1991
			CA 2024723 A1	13-03-1991
			DE 69008282 D1	26-05-1994
			DE 69008282 T2	04-08-1994
			EP 0418065 A2	20-03-1991
			NO 903967 A	13-03-1991
			NZ 235204 A	25-02-1992
			US 5116979 A	26-05-1992
US 5232923	A	03-08-1993	JP 1238524 A	22-09-1989
			JP 1963633 C	25-08-1995
			JP 6096520 B	30-11-1994
			JP 1984716 C	25-10-1995
			JP 2053767 A	22-02-1990
			JP 7020929 B	08-03-1995
			AU 602628 B2	18-10-1990
			AU 3144389 A	21-09-1989
			DE 68917499 D1	22-09-1994
			DE 68917499 T2	09-02-1995
			DK 130389 A	19-09-1989
			EP 0333522 A2	20-09-1989
			FI 891227 A	19-09-1989
			KR 9108665 B1	19-10-1991
			NO 891191 A	19-09-1989

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte. onal Application No

PCT/US 01/04210

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5232923	A	NZ 228329 A	23-12-1991
		JP 1942043 C	23-06-1995
		JP 2152950 A	12-06-1990
		JP 6078286 B	05-10-1994
US 4374990	A	DE 2157424 A1	24-05-1973
	22-02-1983	DE 2240665 A1	07-03-1974
		AT 336625 B	10-05-1977
		AT 469674 A	15-09-1976
		AT 327207 B	26-01-1976
		AT 469774 A	15-04-1975
		AT 336626 B	10-05-1977
		AT 923274 A	15-09-1976
		AT 327203 B	26-01-1976
		AT 981272 A	15-04-1975
		BE 791501 A1	17-05-1973
		CA 1025866 A1	07-02-1978
		CH 613202 A5	14-09-1979
		CH 612430 A5	31-07-1979
		CH 592080 A5	14-10-1977
		CH 590265 A5	29-07-1977
		ES 408565 A1	01-11-1975
		FR 2160611 A1	29-06-1973
		GB 1407854 A	24-09-1975
		JP 1004705 C	30-06-1980
		JP 52053871 A	30-04-1977
		JP 54040555 B	04-12-1979
		JP 52053872 A	30-04-1977
		JP 55019219 B	24-05-1980
		JP 52053873 A	30-04-1977
		JP 57060350 B	18-12-1982
		JP 1032329 C	29-01-1981
		JP 48061484 A	28-08-1973
		JP 55023831 B	25-06-1980
		NL 7215416 A ,B,	22-05-1973
		SE 408423 B	11-06-1979
		US 4115569 A	19-09-1978